Amendments to the Specification

Please replace the paragraph beginning at page 10, line 10 with the following amended paragraph:

~~Fig. 1 is~~ Figs. 1a to 1d depict the complete nucleotide and amino acid sequences (SEQ ID NO:1 and SEQ ID NO:2, respectively) of the *Xenopus laevis* high-affinity melatonin receptor gene coding region cDNA. The deduced amino acid sequence of the receptor is provided below the nucleotide sequence (reading frame b) and contains 420 amino acids. The deduced amino acid sequence begins at nucleotides 32, 33, 34 (ATG = Met) and ends with nucleotides 1292, 1293, 1294 (TGA = stop).

Please replace the paragraph beginning at page 10, line 18 with the following amended paragraph:

~~Fig. 2 is~~ Figs. 2a to 2c depict the complete nucleotide and amino acid sequences (SEQ ID NO:3 and SEQ ID NO:4, respectively) of the sheep high-affinity melatonin-1a receptor gene coding region which is a genetic fusion of genomic DNA from the 5' region and cDNA from the 3' region as described below. The deduced amino acid sequence of the receptor is provided below the nucleotide sequence and contains (reading [[fame]] frame a) 366 amino acids. The deduced amino acid sequence begins at nucleotides 49, 50, 51 (ATG = Met) and ends at nucleotides 1147, 1148, 1149 (TAA = stop).

Please replace the paragraph beginning at page 10, line 28 with the following amended paragraph:

~~Fig. 3 is~~ Figs. 3a to 3c depict the complete nucleotide and amino acid sequences (SEQ ID NO:13 and SEQ ID NO:14, respectively) of the mouse high-affinity melatonin-1a receptor gene coding region. The deduced amino acid sequence of the receptor is provided below the nucleotide sequence and contains (reading frame a) 353 amino acids. The deduced amino acid

sequence begins at nucleotides 1-3 (ATG = Met) and ends at nucleotides 1060-1062 (TAA = stop).

Please replace the paragraph beginning at page 11, line 5 with the following amended paragraph:

~~Fig. 4 is~~ Figs. 4a and 4b depict the nucleotide and deduced amino acid sequences (SEQ ID NO:5 and SEQ ID NO:6, respectively) of a fragment of the human high-affinity melatonin receptor gene coding region genomic DNA. The coding sequence corresponds to the region downstream (3') of the first intron. From the sequenced portion of the receptor DNA, the deduced amino acid sequence is provided below the nucleotide sequence (reading frame a) and contains 288 amino acids. The coding region of the partial sequence begins at nucleotides 1, 2, 3 (GGA = Gly) and ends at nucleotides 865, 866, 867 (TAA = stop).

Please replace the paragraph beginning at page 11, line 16 with the following amended paragraph:

~~Fig. 5 is~~ Figs. 5a to 5c depict the complete nucleotide and amino acid sequences (SEQ ID NO:11 and SEQ ID NO:12, respectively) of the human high-affinity melatonin receptor cDNA. The deduced amino acid sequence of the receptor is provided below the nucleotide sequence (reading frame c) beginning at nucleotides 33-35 (ATG = Met) and contains 350 amino acids ending at nucleotides 1083-1085 (TAA = stop).

Please replace the paragraph beginning at page 11, line 23 with the following amended paragraph:

~~Fig. 6 is~~ Figs. 6a to 6c depict the complete nucleotide and amino acid sequences (SEQ ID NO:15 and SEQ ID NO:16, respectively) of the human high-affinity melatonin-1b receptor cDNA. The deduced amino acid sequence of the receptor is provided below the nucleotide

sequence (reading frame a) beginning at nucleotides 13-15 (ATG = Met), ending at nucleotides 1096-1098 (TAA = stop) and contains amino 362 acids.

Please replace the paragraph beginning at page 12, line 16 with the following amended paragraph:

Figs. 10a and 10b show ^{125}I-melatonin binding assay results from COS-7 cells containing *Xenopus* melatonin receptor cDNA. ~~Fig. 11a~~ Fig. 10a shows a saturation curve. Nonspecific binding was determined using 10 μM melatonin. ~~Fig. 11b~~ Fig. 10b shows a single representative Scatchard plot of the saturation data for determining the relative ^{125}I-melatonin binding constants for the transfected high-affinity melatonin receptor gene from *Xenopus*.

Please replace the paragraph beginning at page 13, line 13 with the following amended paragraph:

~~Fig. 14 shows~~ Figs. 14a and 14b show ^{125}I-melatonin binding assay results from COS-7 cells containing sheep melatonin receptor cDNA. Fig. 14a shows a saturation curve. Nonspecific binding was determined using 10 μM melatonin. Fig. 14a (inset) shows a Scatchard plot of the saturation data for determining the relative ^{125}I-melatonin binding constants for the transfected high-affinity melatonin receptor gene from sheep. The K_d value for the sheep melatonin high-affinity receptor is 3.6×10^{-11} M and the B_{max} value is 104 fmol/mg protein. Nonspecific binding was determined using 10 μM melatonin. Data shown are representative of three experiments. Fig. 14b is a plot of competition by various ligands for ^{125}I-Mel binding in COS-7 cells transfected with the sheep melatonin receptor cDNA (SEQ ID NO:3). Cells were incubated with 100 pM ^{125}I-Mel and various concentrations of 2-iodomelatonin (I-Mel), melatonin (Mel), 6-chloromelatonin (6Cl-Mel), 6-hydroxymelatonin (6OH-Mel), N-acetyl-5-hydroxytryptamine (NAS), or 5-hydroxytryptamine (5-HT). Nonspecific binding was determined in the presence of 10 μM melatonin. K_i values for the sheep receptor are: I-Mel, 3.7×10^{-11} M; Mel, 2.4×10^{-10} M; 6Cl-Mel, 2.5×10^{-10} M; 6OH-Mel, 3.0×10^{-9} M; NAS, 1.4×10^{-7} M; 5HT, $>1.0 \times 10^{-4}$ M. Inhibition curves were generated by LIGAND (Munson, P.L. and Rodbard, D. Anal. Biochem.

(1980) 107:220-239) using a one-site model. The data shown are representative of at least three experiments. 2-Iodomelatonin is available from Research Biochemicals Inc., Natick, MA; 6-chloromelatonin is available from Ely Lily, Indianapolis, IN; all other drugs used herein are available from Sigma, St. Louis, MO.

Please replace the paragraph beginning at page 14, line 10 with the following amended paragraph:

~~Fig. 15 shows~~ Figs. 15a and 15b show ^{125}I-melatonin binding assay results from COS-7 cells containing the complete human melatonin 1a receptor cDNA (SEQ ID NO:11). Fig. 15a shows a saturation curve. Fig. 15a (inset) shows Scatchard plot of the saturation data for determining the relative ^{125}I-melatonin binding constants for the transfected high-affinity melatonin receptor gene from human. The K_d value for the human high-affinity melatonin 1a receptor is 2.6×10^{-11} M and the B_{max} value is 220 fmol/mg protein. Nonspecific binding was determined using 10 μM melatonin. Data shown are representative of three experiments. ~~Fig. 16b~~ Fig. 15b is a plot of competition by various ligands for ^{125}I-Mel binding in COS-7 cells transfected with the human melatonin receptor cDNA (SEQ ID NO:11). Cells were incubated with 100 pM ^{125}I-Mel and various concentrations of 2-iodomelatonin (I-Mel), melatonin (Mel), 6-chloromelatonin (6Cl-Mel), 6-hydroxymelatonin (6OH-Mel), N-acetyl-5-hydroxytryptamine (NAS), or 5-hydroxytryptamine (5-HT). Nonspecific binding was determined in the presence of 10 μM melatonin. K_i values for the human receptor are: I-Mel, 1.8×10^{-11} M; Mel, 2.3×10^{-10} M; 6Cl-Mel, 2.0×10^{-9} M; 6OH-Mel, 2.0×10^{-9} M; NAS, 1.7×10^{-7} M; 5HT, $>1.0 \times 10^{-4}$ M. Inhibition curves were generated by LIGAND (Munson and Rodbard (1980), supra) using a one-site model. The data shown are representative of at least three experiments.

Please replace the paragraph beginning at page 15, line 3 with the following amended paragraph:

~~Fig. 16 is~~ Figs. 16a and 16b are the results of studies showing that recombinant mammalian melatonin receptor couples to G_i. Fig. 16a shows melatonin inhibition of forskolin-

stimulated cAMP accumulation in NIH 3T3 cells stably transfected with the sheep melatonin receptor cDNA (SEQ ID NO:3). The 100% value is the mean cAMP value induced with 10 μM forskolin. The data shown are representative of four experiments. Fig. 16b shows that pertussis toxin blocks the ability of melatonin to inhibit forskolin-stimulated cAMP accumulation in NIH 3T3 cells stably transfected with the sheep melatonin receptor cDNA (SEQ ID NO:3). Cells were preincubated with either vehicle or pertussis toxin for 18 hours (PTX: 100 ng/ml; pertussis toxin was purchased from List, Campbell, CA). C, Basal levels; F, 10 μM forskolin alone; FM, 10 μM forskolin plus 1 μM melatonin. Data are the mean plus standard deviation for 3 plates for each treatment. The data shown are representative of three experiments.

Please replace the paragraph beginning at page 15, line 20 with the following amended paragraph:

~~Fig. 17 shows~~ Figs. 17a, 17b and 17c show a coronal section through the base of the sheep brain and pituitary. Fig. 17a is a histographic staining of the tissue section showing the pars tuberalis (PT) and the pars distalis (PD). Fig. 17b is a film autoradiographic image produced from a section to which [^{125}I]MEL binding is observed in the PT. Fig. 17c is a film autoradiographic image produced from an *in situ* hybridization of a tissue section using a sheep high-affinity melatonin receptor riboprobe derived from the cloned receptor sequence. The hybridization pattern shows that mRNA which hybridizes to the sheep high-affinity melatonin receptor riboprobe exhibits the same pattern of expression as the endogenous receptor protein.

Please replace the paragraph beginning at page 16, line 1 with the following amended paragraph:

~~Fig. 18 is a diagram of the structure of the human Mel-1b receptor protein.~~ Fig. 18a is the predicted membrane topology of the human Mel-1b receptor protein. Y, Potential N-linked glycosylation site. Amino acids that are shaded are identical between human Mel-1b and the human Mel-1a melatonin receptors. Fig. 18b is a comparison of the deduced amino acid sequence of human Mel-1b and the human Mel-la melatonin receptor (GenBank ~~accesssion~~ accession no. U14109) and the Xenopus melatonin receptor (U09561). To maximize homologies, gaps (dots) have been introduced into the three sequences. The seven presumed transmembrane

domains (I-VII) are overlined. Consensus sites for N-linked glycosylation are underlined. The human ~~melaton~~ melatonin 1b receptor sequence has been deposited in GenBank under accession number U25341.